Clinical trial results:
The MIRAD study - Mineralocorticoid Receptor Antagonists in Type 2 Diabetes.
A randomised, double-blind, placebo-controlled study of the effect of Mineralocorticoid Receptor Antagonists in Type 2 Diabetes on glucose and fat metabolism, myocardial function and vascular function.

Summary

EudraCT number	2015-002519-14
Trial protocol	DK
Global end of trial date	10 November 2017

Results information

Result version number	v1 (current)
This version publication date	02 May 2020
First version publication date	02 May 2020

Trial information

Trial identification

Sponsor protocol code	2015-775

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02809963
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Herlev Hospital
Sponsor organisation address	Herlev ringvej 75, Herlev, Denmark, 2730
Public contact	Forskingsenheden, Herlev Hospital, caroline.michaela.kistorp@regionh.dk
Scientific contact	Forskingsenheden, Herlev Hospital, caroline.michaela.kistorp@regionh.dk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 March 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 November 2017
Global end of trial reached?	Yes
Global end of trial date	10 November 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective to investigate the effect of Eplerenone 200 mg once daily compared to placebo on:
- Liver fat content by proton MR spectroscopy

Protection of trial subjects:

All participants were informed orally and in written form and gave their written consent prior to randomization.
The study was conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice (GCP) and monitored by the GCP unit Bispebjerg, Copenhagen, Denmark, and in accordance with the Declaration of Helsinki and approved by the Danish Medicines Agency and the Regional Scientific Ethics Committee of the Capital region of Denmark.

Background therapy:

Patients with type 2 diabetes and the presence of or high risk of cardiovascular disease were randomized to either eplerenone or placebo in addition to standard care therapy. Study medication (eplerenone/placebo) was administered as an add-on treatment to background therapy, and the protocol dictated that the investigators should adjust doses of the study medication in accordance with measurements of potassium and creatinine. Therefore, no downregulations in angiotensin-converting-enzyme (ACE)-inhibitor or angiotensin II receptor blocker (ARB) treatment were allowed prior to randomization or during the study.

Evidence for comparator:

The design of the study was a randomized-double-blinded-placebo-controlled trial.
Placebo vs active (eplerenone) treatment.

Actual start date of recruitment	19 October 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 140
Worldwide total number of subjects	140
EEA total number of subjects	140

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	70
From 65 to 84 years	70
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients with type 2 diabetes and the presence of or high risk of cardiovascular disease were randomized to either eplerenone or placebo in addition to standard care therapy between November 2015 and November 2017.

Pre-assignment

Screening details:

Key inclusion criteria were type 2 diabetes diagnosed at least 3 months prior to enrolment and known cardiovascular disease or NT-proBNP ≥ 70 ng/L or albuminuria . Key exclusion criteria were left ventricular ejection fraction < 40%, plasma potassium ≥ 5.0 mmol/L at screening, severe liver disease, or impaired kidney function eGFR < 40 ml/min/1.73m

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

Patients were randomized in blocks of ten 1:1 (eplerenone: placebo). Study treatment allocation was generated electronically and secured by the central pharmacy, Glostrup, Copenhagen, Denmark, which was not otherwise involved in patient randomization procedures. The central pharmacy packed and labeled the study medications.

Arms

Are arms mutually exclusive?	Yes
Arm title	active

Arm description:

Eplerenone treatment, a selective mineralocorticoid receptor antagonist, was the active arm.

Arm type	Experimental
Investigational medicinal product name	eplerenon
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were randomized to either eplerenone 100–200 mg once daily or placebo for 26 weeks. Study medication treatment followed a fixed-dose titration protocol, with a starting dose of 50 mg increasing to a maximum dose of 200 mg for patients with a baseline eGFR ≥60 ml/min/1.73m2 and 100 mg for patients with a baseline eGFR 40–59 ml/min/1.73m2. The protocol dictated titration with 50 mg every second week in patients without adverse effects to the maximum dose at the 8-week visit. Plasma potassium and creatinine were measured according to the protocol at baseline and every second week before dose adjustment.

Arm title	placebo

Arm description:

placebo was used to compare with eplerenone treatment (the active arm)

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were randomized to either eplerenone 100–200 mg once daily or placebo for 26 weeks. Study medication treatment followed a fixed-dose titration protocol, with a starting dose of 50 mg increasing to a maximum dose of 200 mg for patients with a baseline eGFR ≥60 ml/min/1.73m2 and 100 mg for patients with a baseline eGFR 40–59 ml/min/1.73m2. The protocol dictated titration with 50 mg every second week in patients without adverse effects to the maximum dose at the 8-week visit. Plasma potassium and creatinine were measured according to the protocol at baseline and every second week before dose adjustment.

Number of subjects in period 1	active	placebo
Started	70	70
Completed	65	64
Not completed	5	6
Consent withdrawn by subject	3	6
Adverse event, non-fatal	2	-

Baseline characteristics

Reporting groups	
Reporting group title	active
Reporting group description:	
Eplerenone treatment, a selective mineralocorticoid receptor antagonist, was the active arm.	
Reporting group title	placebo
Reporting group description:	
placebo was used to compare with eplerenone treatment (the active arm)	

Reporting group values	active	placebo	Total
Number of subjects	70	70	140
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Patients between 18-85 years were included			
Units: years			
arithmetic mean	64.1	62.7	
standard deviation	± 8.7	± 10.0	-
Gender categorical Units: Subjects			
Female	17	20	37
Male	53	50	103
Liver fat content at baseline			
120 patients completed MR-spectroscopy at baseline. 62 patients in the eplrenone group and 58 patients in th eplacebo			
Units: percentage			
median	5.8	3.5	
inter-quartile range (Q1-Q3)	1 to 12.6	1 to 11.2	-

End points

End points reporting groups

Reporting group title	active
Reporting group description:	
Eplerenone treatment, a selective mineralocorticoid receptor antagonist, was the active arm.	
Reporting group title	placebo
Reporting group description:	
placebo was used to compare with eplerenone treatment (the active arm)	

Primary: Liver fat content

End point title	Liver fat content
End point description:	
End point type	Primary
End point timeframe:	
Change from baseline to end of study (week 26)	

End point values	active	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	48		
Units: percentage				
arithmetic mean (confidence interval 95%)	0.91 (-0.57 to 2.39)	-1.01 (-2.23 to 0.21)		

Statistical analyses

Statistical analysis title	mixed model with repeated visit statement
Statistical analysis description:	
Analyses were performed using a mixed model with repeated visit statement, handling missing data using a maximum likelihood	
Comparison groups	active v placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	≤ 0.05
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.92

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	3.81
Variability estimate	Standard deviation

Notes:

[1] - not applicable

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event were recorded from the day of randomization to two weeks after end of study = time period of adverse events.
Patients were asked about adverse events at every visit including telephone visit (week 2, 4, 6, 8, 10, 14, 18, 22, 26).

Adverse event reporting additional description:

See above

Assessment type	Systematic

Dictionary used

Dictionary name	GCP-unit
Dictionary version	F3-2013

Reporting groups

Reporting group title	active

Reporting group description:

Eplerenone treatment, a selective mineralocorticoid receptor antagonist, was the active arm.

Reporting group title	placebo

Reporting group description:

placebo was used to compare with eplerenone treatment (the active arm)

Serious adverse events	active	placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 70 (2.86%)	4 / 70 (5.71%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Surgical and medical procedures			
Amputation			
subjects affected / exposed	0 / 70 (0.00%)	2 / 70 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 70 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Dizziness postural			

subjects affected / exposed	1 / 70 (1.43%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea	Additional description: COPD in exacerbation		
subjects affected / exposed	1 / 70 (1.43%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
nefrolithiasis			
subjects affected / exposed	1 / 70 (1.43%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Erysipelas			
subjects affected / exposed	0 / 70 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	active	placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 70 (57.14%)	26 / 70 (37.14%)	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 70 (0.00%)	3 / 70 (4.29%)	
occurrences (all)	0	3	
Blood and lymphatic system disorders			
hyperkaliemia	Additional description: Hyperkaliemia was defined as K+≥ 5.5 mmol/ and severe hyperkaliemia as K+≥ 6.0 mmol/L. No patients experienced severe hyperkaliemia.		
subjects affected / exposed	6 / 70 (8.57%)	2 / 70 (2.86%)	
occurrences (all)	10	2	
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	4 / 70 (5.71%)	3 / 70 (4.29%)	
occurrences (all)	4	3	
Ear and labyrinth disorders			
Dizziness postural			
subjects affected / exposed	3 / 70 (4.29%)	2 / 70 (2.86%)	
occurrences (all)	3	2	
Gastrointestinal disorders			
Abdominal discomfort	Additional description: conmstipation, diarrhea, feeling bloated		
subjects affected / exposed	10 / 70 (14.29%)	7 / 70 (10.00%)	
occurrences (all)	10	7	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	3 / 70 (4.29%)	1 / 70 (1.43%)	
occurrences (all)	3	1	
Renal and urinary disorders			
Polyuria			
subjects affected / exposed	3 / 70 (4.29%)	4 / 70 (5.71%)	
occurrences (all)	3	4	
Creatinine renal clearance decreased	Additional description: increased creatinine > 30%		
subjects affected / exposed	2 / 70 (2.86%)	2 / 70 (2.86%)	
occurrences (all)	2	2	
Endocrine disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 70 (1.43%)	0 / 70 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Muscle discomfort	Additional description: e.g leg cramps		
subjects affected / exposed	5 / 70 (7.14%)	0 / 70 (0.00%)	
occurrences (all)	5	0	
Arthralgia			
subjects affected / exposed	3 / 70 (4.29%)	1 / 70 (1.43%)	
occurrences (all)	3	1	
Wound complication	Additional description: diabetic foot ulcers		
subjects affected / exposed	0 / 70 (0.00%)	1 / 70 (1.43%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31183945